

# Mortality Experience in Relation to a Measured Arsenic Trioxide Exposure

by Sherman S. Pinto,\* Philip E. Enterline,\*  
Vivian Henderson,\* and Michael O. Varner\*

This report examines the mortality experience of 527 men who retired from a copper smelter where they were exposed to airborne arsenic trioxide. Urinary arsenic values of all plant employees were determined in 1973, and the relative arsenic exposure in the various departments of the plant were determined. The relationship of airborne arsenic concentrations to urinary arsenic values was studied in a separate experiment, and the feasibility of using urinary arsenic values as a measure of arsenic exposure was established.

The mortality experience of the cohort under study showed them to have a mortality 12.2% higher than was found for males of the same area at the same ages and in the same time period. The excess mortality was due chiefly to respiratory cancer. When the deaths were classified by total lifetime arsenic exposure, the respiratory cancer mortality was linearly related to the amount of exposure. The 1973 figures for arsenic exposure underestimated the exposure of the cohort group by a factor of possibly 10. Evidence was obtained which suggests that after removal from arsenic exposure, the risk of lung cancer declines.

Certain of the data which are presented suggests there may be a threshold value for airborne arsenic trioxide exposure below which no adverse effects may be expected.

This is a study of the causes of death among a group of 527 pensioners in a copper smelter who were alive on January 1, 1949. A previous study on mortality in this smelter has been reported (1).

The group consisted of all men who were pensioners and living on January 1, 1949 plus those who became pensioners before January 1, 1973. Deaths occurring in the group were tabulated through December 31, 1973. The plant handles large quantities of arsenic trioxide, and this factor has been carefully evaluated in the study.

Death certificates were obtained for all those of the group who died, and the causes of death were coded by an independent nosologist. The expected mortality was based on the experience of the male population in the State of Washington living in the time-interval which characterized the study population. Causes of death were coded to the 7th Revision of the International Classification of Diseases (2) for all years. Expected deaths in the period 1969-1973, when the 8th Revision of the International Classification of Diseases (3) was in effect, were estimated by extrapolation from prior years.

A total of 527 men in this study reached age 65, and all were exposed to arsenic trioxide to some degree during the course of their work in the smelter.

Complete job histories were available for 525 men. The average duration of employment for these 525 men was 28 yr, and the range of employment ranged from 7 to 54 years.

The question of how much exposure to arsenic these individuals had was examined as carefully as possible. For a number of years the arsenic content of the urine has been used in this plant as a measure of arsenic exposure. This was done because many of the men work at jobs which require them to wear a respirator. The urinary arsenic value is a measure of the effectiveness of personal protective equipment if such is used. If none is needed, the urinary value is a continuing check on personal exposure.

With the development of the personal sampler we were able to study the relationship between airborne arsenic trioxide and urinary arsenic (4). Twenty-four workers regularly exposed to airborne arsenic trioxide during the course of their work wore personal air samplers for five successive days. No respirators were worn by any of these in-

\*ASARCO Inc., P. O. Box 1677, Tacoma, Washington 98401.

dividuals during the test period. Urine samples were collected from each of the 24 workers who wore personal monitors for 2 days prior to the work week, each day during the work week, and for 3 days afterward. In other work we have found eating certain fish can result in the excretion of arsenic compounds into the urine. Unless this extraneous source of arsenic is controlled, erroneously high results will be obtained. All individuals in this study were asked to refrain from eating fish 2 days preceding the study and during the course of the study itself.

The average airborne arsenic concentration ranged from 3 to 295  $\mu\text{g}/\text{m}^3$ , and the overall airborne arsenic mean concentration was 53  $\mu\text{g}/\text{m}^3$ . The average urinary arsenic values ranged from 38 to 539  $\mu\text{g}/\text{l}$ , with an overall average of 174  $\mu\text{g}/\text{l}$ .

A fairly good correlation was found between airborne arsenic concentrations and urinary arsenic levels over the range studied. The study showed exposure to arsenic trioxide is reflected in the worker's urine within 24 hr. Therefore, biological monitoring of urinary arsenic can be directly related to airborne arsenic trioxide.

The relationship between arsenic concentrations and urinary arsenic levels over the range studied are shown in Figure 1.

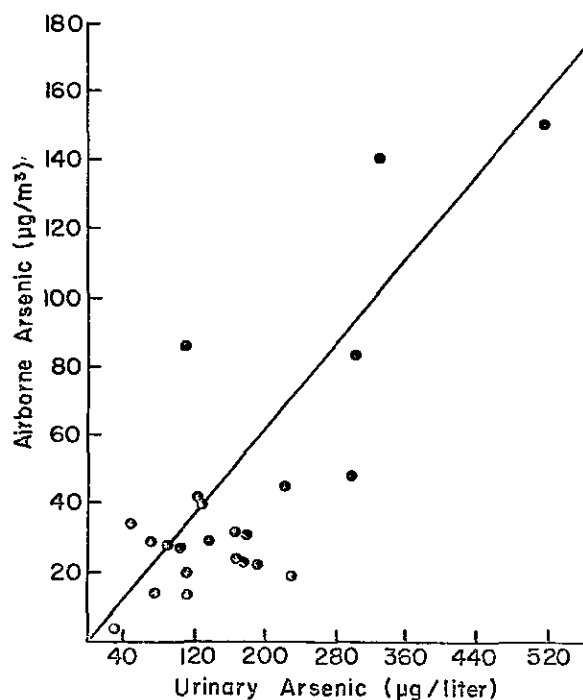


FIGURE 1. Relationship between urinary arsenic excretion and concentration of inhaled arsenic. Correlation, 0.530; significance,  $p < 0.01$ ; regression,  $Y = 0.304X$ ; standard error of estimate, 55. Note: one data point (224,295) not shown.

In using urinary arsenic values it is also important to remember a small amount of arsenic is always present in the urine. We analyzed the urine of 204 people applying for employment in 1973–1974. These were principally young men. The average urinary arsenic value of this entire group was 52.6  $\mu\text{g}/\text{l}$ , and none of these individuals gave any history of industrial arsenic exposure during the preceding 3 yr.

In 1973, a urinary arsenic determination was made for each person in the plant being studied. Employment usually is about 1000 people. From these figures, the average urinary arsenic value for each of the 33 departments was calculated. The overall average urinary arsenic value for the entire plant was 223  $\mu\text{g}/\text{l}$ .

There are insufficient historic data available to make possible the direct determination of the exposure of each of the 525 retirees during his working life. However, by using the average urinary arsenic value for each of the 33 departments, determined as described above, an index of exposure was constructed for each retiree for comparative purposes. In the construction it is assumed that there is a direct relationship between urinary arsenic and exposure to airborne arsenic, as illustrated in Figure 1. It is also assumed that while the magnitudes of exposures in all departments have changed over time, the relative exposure between and among departments have been approximately constant through the years. The average urinary arsenic value for a department as determined in 1973 was multiplied by the time in years that a retiree had spent in that department; for that man the same calculation was made for each department in which he had worked and the sum of all the products so obtained for that man was found. This was called the man's "exposure index"; it is not a measure in any kind of unit of the man's total exposure to arsenic but is a representation for comparison purposes. When the exposure index for a particular retiree obtained in this way is divided by the total number of years worked by him, the result is a figure that represents the intensity of his life-time exposure to airborne arsenic; it is not a measure of the intensity, only an index for comparison purposes.

The indices discussed above, it is emphasized, are based upon urinary arsenic values in 1973 rather than upon actual exposures in any year. Actual exposures took place during the interval 1910–1973. The median of this work experience occurred in 1938. The middle 50% of the group's work experience occurred during the period 1928–1947.

Scattered air analyses for arsenic were made irregularly during the late 1930's and early 1940's. These data indicate the airborne arsenic exposure

in that early period may have been from 5 to 10 times as much as was found in 1973. The interpretation of health effects of arsenic therefore cannot be based on air concentrations found in 1973, but must be considered as having been caused by larger amounts of airborne arsenic.

Table 1 presents the observed and expected numbers of deaths at age 65 and over, and standardized mortality ratios (SMR) for selected causes of death for the entire cohort of 527 men. When the observed and expected number of deaths are the same, the SMR would be 100, and deviations from 100 can be interpreted as percentage deviations from expected mortality.

**Table 1. Observed and expected deaths and SMR for selected causes of death, 527 males retiring from a copper smelting plant who were living January 1, 1949 and followed through 1973.**

Cause of death	No.		SMR
	Observed	Expected	
All causes	324	288.7	112.2 <sup>a</sup>
Cancer (140-205)	69	46.5	148.4 <sup>a</sup>
Digestive (150-159)	20	16.4	122.0
Respiratory (160-164)	32	10.5	304.8 <sup>a</sup>
Lymph, etc. (200-203, 205)	2	2.1	95.2
Urinary (180, 181)	3	3.3	90.9
All other cancers	12	14.2	84.5
Stroke (330-334)	43	38.0	113.2
Heart disease (400-443)	144	132.3	108.8
Coronary heart disease (420)	120	110.2	108.9
All other heart disease	24	22.1	108.6
Respiratory disease (480-493, 500-502)	11	10.8	101.8
All other causes	57	61.8	92.2

<sup>a</sup>*p* < 0.05.

Table 1 shows that men who retired from the smelter and had been exposed to airborne inorganic arsenic had an overall mortality rate 12.2% higher than all Washington males. This excess is due principally to cancer of the respiratory system. There was also some excess cancer of the digestive system.

It is noteworthy that, although much of the body burden of arsenic is eliminated in the urine, there is no increase in cancer of the urinary tract. This would seem to indicate that the body has a fairly successful detoxification mechanism for handling inorganic trivalent arsenic.

The question of cigarette smoking as it might relate to respiratory cancer excess was also studied. Smoking histories were obtained from all living pensioners and from relatives of most men who had died since January 1, 1961. Arsenic workers who were smokers had their mortality experience compared with expected deaths for all smokers in the State of Washington (5). Similar comparisons were

made for ex-smokers and nonsmokers in the state. The elevated SMR for respiratory cancer does not seem to be due to smoking in the study population.

Table 2 shows the relationship between the arsenic exposure index and mortality due to respiratory cancer. The actual mean for each class in the Index is given in parentheses. If the mean exposure index is plotted against the SMR on arithmetic paper there is shown a trend which is roughly linear.

**Table 2. Observed and expected respiratory cancer deaths and SMR by arsenic exposure index.**

Exposure index (mean index)	No. of men	Respiratory cancer deaths		
		Observed	Expected	SMR
<2000 (1514)	36	1	0.9	111.1
2000-2999 (2513)	109	4	2.1	190.5
3000-5999 (4317)	205	11	3.9	282.0 <sup>a</sup>
6000-8999 (7473)	109	7	2.3	304.3 <sup>a</sup>
9000-11,999 (10,135)	38	4	0.7	571.4 <sup>a</sup>
>12,000 (14,712)	29	5	0.6	833.3 <sup>a</sup>

<sup>a</sup>*p* < 0.05.

The next step was to consider the two components of the exposure index, that is, duration and intensity of exposure. Both duration of exposure and intensity of exposure make a contribution to the excess respiratory cancer. Table 3 shows the incidence of lung cancer in relation to intensity and duration of exposure. Analyses of these data show that intensity of exposure holding constant for duration is a better predictor of lung cancer than is duration of exposure holding constant for intensity.

**Table 3. Observed and expected respiratory cancer deaths and standardized mortality ratios by intensity and duration of exposure.**

Intensity of exposure, μg/l. urine	Duration of exposure					
	<25 yr			≥25 yr		
	Obs	Exp	SMR	Obs	Exp	SMR
50-199	2	2.1	95.2	10	3.6	277.8 <sup>a</sup>
200-349	4	1.5	266.7	8	2.2	363.6 <sup>a</sup>
≥350	3	0.5	600.0 <sup>a</sup>	5	0.6	833.3 <sup>a</sup>

<sup>a</sup>*p* < 0.05.

Table 4 shows the number of men studied and person-years lived by duration and intensity of exposure. Tables 3 and 4 in conjunction show a low SMR for 99 men exposed for less than 25 yr to levels of airborne arsenic that produced mean urinary arsenic levels between 50 and 199 μg/l. While numbers are small and only two respiratory cancer deaths were observed, person-years lived in this exposure is fairly large and similar to other groups. One explanation for the low SMR of men exposed less than 25 yr prior to retirement is that insufficient

**Table 4. Number in cohort and person-years lived in follow-up period by intensity and duration of exposure.**

Intensity of Exposure, $\mu\text{g/l. urine}$	Duration of exposure			
	<25 yr		$\geq 25$ yr	
	No. of men	Person-years lived	No. of men	Person-years lived
50-199	99	856.8	191	1534.8
200-349	76	659.3	106	949.2
$\geq 350$	25	185.4	28	222.0

time may have elapsed for cancer to be observed. On the other hand, there is a distinct possibility that the passage of time after termination of exposure may result in a decline of effect (6). For cigarette smokers in the general population, it is generally accepted that lung cancer risks come close to normal roughly 10 years following the cessation of smoking. In the case of chromate workers, also, there is a decline with time after the termination of exposure (7).

Table 5 shows that respiratory cancer risk declined with increasing age in the group under study. Since arsenic exposure stopped for all individuals at age 65, the figures indicate the effect of past arsenic exposures disappear. These observations also indicate there is a threshold of safety for arsenic trioxide exposure as measured by the urinary arsenic value (8). Further analyses of these and other data are being made to more clearly establish the level of such a threshold.

**Table 5. Observed and expected respiratory cancer deaths and standardized mortality ratios by age.**

Age	Respiratory cancer deaths		
	Observed	Expected	SMR
65-69	14	4.1	341.4 <sup>a</sup>
70-74	11	3.5	314.3 <sup>a</sup>
75-79	5	2.0	250.0
$\geq 80$	2	1.0	200.00

<sup>a</sup> $p < 0.05$ .

## Summary

Urinary arsenic values were determined for 24 men exposed to arsenic trioxide at work. The airborne arsenic trioxide concentration to which each of the men had been exposed was measured by a personal sampler. A direct correlation between airborne arsenic and urinary arsenic values was found in the range studied.

This report examines the mortality experience of 527 men who retired from a copper smelter where they were exposed to airborne arsenic trioxide. The men retired prior to January 1, 1973. An index of arsenic exposure was calculated for each on the basis of urinary arsenic values.

Overall mortality of this cohort was 12.2% higher than for males of the same area, at the same ages and in the same time period. The excess mortality was due chiefly to respiratory cancer which was three times the expected and was not due to cigarette smoking.

A time-weighted index of total lifetime exposure was linearly related to respiratory cancer mortality and ranged from an SMR of 111.1 at the lowest exposure to 833.3 at the highest.

Evidence was obtained which suggests that after removal from arsenic exposure, the risk of cancer of the lungs declines.

Other airborne contaminants were present in the atmosphere of this smelter, and their possible effect on producing lung cancer is uncertain. However, it is highly likely that airborne arsenic trioxide is closely related to the process.

Certain of the data which have been presented suggests there may be a threshold value for airborne arsenic trioxide exposure below which no adverse effects may be expected. Further work on establishing this threshold is continuing.

## REFERENCES

1. Pinto, S. S., and Bennett, B. M. Effect of arsenic trioxide exposure on mortality. *Arch. Environ. Health*, 7: 583 (1963).
2. World Health Organization. *International Statistical Classification of Diseases, Injuries and Causes of Death*. 7th Revision, WHO, Geneva, 1957.
3. World Health Organization. *Manual of International Statistical Classification of Diseases, Injuries and Causes of Death*. 8th Revision WHO, Geneva, 1965.
4. Pinto, S. S., et al. Arsenic trioxide absorption and excretion in industry. *J. Occup. Med.* 18: 677 (1976).
5. Henderson, V. Estimating the risk of respiratory cancer due to occupational exposure in smokers vs. non-smokers: a method for adjustment.
6. Jones, H. B., and Grendon, A. Environmental factors in the origin of cancer and estimation of the possible hazard to man. *Food Cosmet. Toxicol.* 18: 251 (1975).
7. Enterline, P. E. Respiratory cancer among chromate workers. *Occup. Med.* 16: 523 (1974).
8. World Health Organization. *Assessment of the Carcinogenicity and Mutagenicity of Chemicals*. Technical Report Series, No. 546. WHO Publishers, Geneva, Switzerland, 1974.